

Remarks

Amendments

The specification and claims 1, 25, and 29 were amended to correct obvious typographical errors. Claim 36 has been amended to specify that the magnetic material is in the form of nanoparticles having a number average diameter between 5 nm and 50 nm and the matrix material comprises a protein. Support for this amendment is found at least at original claims 34- 35. No new matter has been added. Claims 1-36 remain pending.

Rejection Under 35 U.S.C. § 112

Claims 1 and 29 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The rejection is respectfully traversed if applied to the claims as amended. The rejection was based on minor, typographical errors, which have now been eliminated.

Rejection Under 35 U.S.C. § 102

Claims 1-8, 13-18, 21, 22, 29-33, 35, and 36 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 4,774,265 to Ugelstad et al. (hereinafter "Ugelstad '265"). The rejection is respectfully traversed.

"A claim is anticipated only if *each and every element* as set forth in the claim is found, *either expressly or inherently described*, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631 (Fed. Cir. 1987). A claim element is not "inherent" in the disclosure of a prior art reference unless extrinsic evidence clearly shows that missing descriptive matter is *necessarily* present in the thing described in the reference. In re Robertson, 49 U.S.P.Q. 1949 (Fed. Cir. 1999). "Inherency, however, may not be established by mere probabilities or possibilities" (49 U.S.P.Q. at 1950-51). As detailed below, each and every

element of Applicants' claims is in fact not explicitly or inherently disclosed in Ugelstad '265.

Accordingly, the reference necessarily fails to anticipate the claimed methods and compositions.

Applicants' Claimed Methods

Applicants developed and claim an encapsulation method that uses a *heat-induced crosslinking* process for forming microparticles. It was found that this approach could yield, for example, microspheres of a heat-stabilized albumin encapsulating maghemite that were more stable and more polydisperse than microspheres made by a chemical cross-linking process (Specification, Page 4, Lines 5-14).

The first step of the claimed method is forming an emulsion that has aqueous microdroplets dispersed in a hydrophobic continuous phase comprising an oil and an oil-soluble surfactant. The microdroplets of this emulsion include *both the agent* (e.g., maghemite) to be encapsulated *and a cross-linkable matrix material*. This step is done at a first temperature that is lower than the temperature effective to initiate cross-linking of the matrix material. The second step of the claimed method is heating the emulsion to cause the matrix material to crosslink, thereby forming the microparticles that comprise the agent encapsulated by the crosslinked matrix material. In a preferred embodiment, the encapsulated agent is a magnetic material in the form of *nanoparticles*.

Ugelstad '265

Ugelstad discloses a method of making magnetic polymer particles that includes the following ordered steps: (1) provide polymer particles as a starting material, (2) combine the polymer particles with an aqueous solution of iron salts, and then (3) adjust the pH of the

aqueous solution to cause the iron hydroxides to precipitate onto surfaces of the polymer particles. See Abstract; col. 7, lines 4-7; col. 4, lines 49-50.

Ugelstad '265 clearly fails, however, to disclose Applicants' claimed process. First, the reference does not disclose a water-in-oil emulsion wherein *the aqueous microdroplets include the agent to be encapsulated* and wherein the microdroplets are dispersed in an oil and an oil soluble surfactant, *before* formation of the polymer particle. In Ugelstad '265, the iron to be encapsulated is not present in a polymeric matrix material until *after* formation of the polymer particles has been completed. The iron of Ugelstad is never present within a microdroplet form of a matrix material in a water-in-oil emulsion, as would be required with Applicants' claims. Nor is there any evidence in Ugelstad '265 that any emulsion *necessarily* is a water-in-oil emulsion wherein the oil phase *necessarily* includes an oil soluble surfactant.

Furthermore, Ugelstad '265 fails to teach a *heat-initiated crosslinking step* after the agent to be encapsulated already has been combined with a cross-linkable matrix material. The only heating taught by Ugelstad '265 is an optional heating step during or following the precipitation of the iron onto surfaces of the pre-made polymer particles, to promote formation of Fe_3O_4 rather than formation of $\text{Fe}(\text{OH})_2$ or $\text{Fe}(\text{OH})_3$ to achieve better magnetization (Col. 6, Lines 9-14) or heating as part of chemically initiated process for polymerizing a monomer emulsion (Col. 7, Lines. 17-22). In the latter case, no agent to be encapsulated is present in either the dispersed phase or continuous phase of the emulsion. In either case, the heating is wholly different from Applicants' methods.

The heating step disclosed in Ugelstad '265 is not heating to effect cross-linking of a matrix material in a microdroplet that includes the agent to be encapsulated, as recited in

Applicants' claims 1, 25, and 29. Consequently, Ugelstad '265 neither explicitly nor inherently discloses heating an emulsion "which comprises aqueous microdroplets, including the agent and a cross-linkable matrix material" as required by Applicants' claims. In addition, Ugelstad '265 discloses nothing about encapsulating nanoparticles, particularly nanoparticles having a size of 5 to 50 nm, as required by Applicants' claim 36.

For all of the foregoing reasons, it is respectfully submitted that Ugelstad '265 indisputably fails to anticipate any of Applicants' claims and that the rejection should be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 9-12, 20, 23-28, and 34 were rejected under 35 U.S.C. § 103 as obvious over Ugelstad '265. Claims 9-12, 23-28, and 34 also were rejected under 35 U.S.C. § 103 as obvious over Ugelstad '265 in view of U.S. Patent No. 5,763,203 to Ugelstad et al. (hereinafter "Ugelstad '203"). The rejections are respectfully traversed.

Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. In re Fritch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); In re Laskowski, 871 F.2d 115 (Fed. Cir. 1989). As detailed below, the Office Action has not established a *prima facie* case of obviousness for Applicants' claims.

Ugelstad '265, alone or in combination with Ugelstad '203, fails to suggest heating to effect cross-linking of a matrix material in a microdroplet that includes the agent to be encapsulated, as required by Applicants' claimed methods. Moreover, Ugelstad '203 is

completely silent on how its magnetic polymeric particles are made. Furthermore, Ugelstad '265 discloses "forming *drops* which contain magnetite and protein" by vigorous stirring in water with an emulsifier (Col. 1, Lines 43-46) but there is no mention of converting these drops into *stable particles* by any means, and particularly not by any kind of *heat induced cross-linking in an oil medium*, as required by Applicants' claim 1 and all claims dependent thereon.

In addition, Ugelstad '265 *as a whole* plainly teaches away from Applicants' claimed methods. For example, it states that "the fact that magnetite is used will, even if it is employed in very finely divided form, *represent great limitations* with respect to the type and the size of the particles. (Col. 1, Lines 50-53). Ugelstad effectively teaches that is undesirable to encapsulate a *solid agent, no matter how small*. He then explains how his invention avoids encapsulating a solid agent by adding the agent *in solution* form to a *pre-made* polymer particle, followed by precipitating the agent into a solid coating on surfaces of the pre-made polymer particle. Consequently, nothing in Ugelstad '265 would have led one of ordinary skill in the art to modify Ugelstad's process to somehow derive Applicants' claimed methods or compositions.

Similarly, nothing in Ugelstad '265 remotely suggests a particular combination composition of microparticles that include a matrix material and an encapsulated magnetic material, wherein (1) the matrix material comprises a protein, (2) the magnetic material is in the form of nanoparticles having a number average diameter between 5 nm and 50 nm, and (3) the microparticles have a number average diameter between about 300 and about 800 nm.

The Office Action therefore does not provide the required clear and particular showing that the prior art as a whole suggests the desirability, and thus the obviousness, of making the claimed combination of elements. That in hindsight of applicants' disclosure a skilled artisan

arguably may be able to recognize, cull, modify, and combine certain claim elements from disparate references is not evidence of a clear and particular motivation to combine those references. *See, e.g., In re Lee*, 61 U.S.P.Q.2d 1430, 1433-34 (Fed. Cir. 2002); *ATD Corp. V. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998) (“Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.”). The motivation required to make the specific modifications to Ugelstad simply has not been shown to exist in Ugelstad ‘265, alone or in combination with Ugelstad ‘203, sufficient to establish a *prima facie* case of obvious.

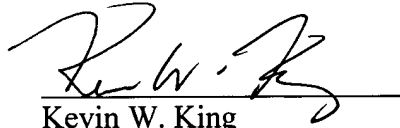
Conclusions

From the foregoing analysis, it is clear that Applicants claims require a combination of steps and specific limitations that are novel over the cited Ugelstad patents. It is also evident that one having ordinary skill in the art would not have been led to take the teaching and Ugelstad and make the substantial changes necessary to derive Applicants’ claimed processes and compositions. Accordingly, no *prima facie* case of obviousness has been established for Applicants’ claims. Applicants therefore submit that the claims are clear and patentable over the prior art of record. Allowance of claims 1-36 is therefore respectfully solicited.

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AMENDMENT &
RESPONSE TO OFFICE ACTION

The undersigned respectfully invites the Examiner to contact him by telephone (404.853.8068) if any outstanding issues can be resolved by conference or examiner's amendment.

Respectfully submitted,



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